



Exhibit 1

Scientific Literature Referring to TLR-4, TLR4, tlr4, or toll-like receptor 4.

1. Poltorak, A., X. He, I. Smirnova, M.-Y. Liu, C. Van Huffel, X. Du, D. Birdwell, E. Alejos, M. Silva, C. Galanos, M. A. Freudenberg, P. Ricciardi-Castagnoli, B. Layton, and B. Beutler. 1998. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in *Tlr4* gene. *Science* 282:2085-2088.
2. Du, X., Poltorak, A., Silva, M., and Beutler, B. Analysis of Tlr4-mediated LPS signal transduction in macrophages by mutational modification of the receptor. *Blood Cells Molecules & Diseases* 25(21), 328-338. 11-8-1999.
3. Frantz, S., Kobzik, L., Kim, Y. D., Fukazawa, R., Medzhitov, R., Lee, R. T., and Kelly, R. A. Toll4 (TLR4) expression in cardiac myocytes in normal and failing myocardium. *J. Clin. Invest.* 104(3), 271-280. 1999.
4. Hoshino, K., O. Takeuchi, T. Kawai, H. Sanjo, T. Ogawa, Y. Takeda, Takeda, and S. Akira. 1999. Cutting edge: Toll-like receptor 4 (TLR4)-deficient mice are hyporesponsive to lipopolysaccharide: Evidence for TLR4 as the Lps gene product. *Journal of Immunology* 162:3749-3752.
5. Qureshi, S. T., L. Larivière, G. Leveque, S. Clermont, K. J. Moore, P. Gros, and D. Malo. 1999. Endotoxin-tolerant mice have mutations in toll-like receptor 4 (Tlr4) [CORRECTION]. *J. Exp. Med.* 189:1519-1520.

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6. Qureshi, S. T., L. Lariviere, G. Leveque, S. Clermont, K. J. Moore, P. Gros, D. Malo, Lipopolysaccharide, Inflammation, c. Positional, Salmonella, and Mice. 1999. Endotoxin-tolerant mice have mutations in toll-like receptor 4 (Tlr4). *J. Exp. Med.* 189:615-625.
7. Shimazu, R., Akashi, S., Ogata, H., Nagai, Y, Fukudome, K., Miyake, K., and Kimoto, M. MD-2, a molecule that confers lipopolysaccharide responsiveness on Toll-like receptor 4. *Journal of Experimental Medicine* 189(11), 1777-1782. 6-7-1999.
8. Takeuchi, O., Hoshino, K., Kawai, T., Sanjo, H., Takada, H., Ogawa, T., Takeda, K., and Akira, S. Differential roles of TLR2 and TLR4 in recognition of Gram-negative and Gram-positive bacterial cell wall components. *Immunity* 11, 443-451. 1999.
9. Akashi, S., R. Shimazu, H. Ogata, Y. Nagai, K. Takeda, M. Kimoto, and K. Miyake. 2000. Cutting edge: cell surface expression and lipopolysaccharide signaling via the toll-like receptor 4-MD-2 complex on mouse peritoneal macrophages [In Process Citation]. *J. Immunol.* 2000. Apr. 1.; 164. (7.): 3471.-5. 164:3471-3475.
10. Arbour, N. C., Lorenz, E., Schutte, B. C., Zabner, J., Kline, J. N., Jones, M., Frees, K., Watt, J. I., and Schwartz, D. A. *TLR4* mutations are associated with endotoxin hyporesponsiveness in humans. *Nature Genetics* 25, 187-192. 2000.
11. Beutler, B. Endotoxin, Toll-like receptor 4, and the afferent limb of innate immunity. *Curr. Opin. Microbiol.* 3(1), 23-28. 2000.

12. Beutler, B. Tlr4: central component of the sole mammalian LPS sensor.
Curr.Opin.Immunol. 12(1), 20-26. 2000.
13. Beutler, B., Smirnova, I., and Poltorak, A. Tlr4: the sole gateway to endotoxin response. Proceedings of the 1st Regensburg Immunology Congress . 2000.
14. Hou,L., H.Sasaki, and P.Stashenko. 2000. Toll-Like Receptor 4-Deficient Mice Have Reduced Bone Destruction following Mixed Anaerobic Infection.
Infect.Immun. 68:4681-4687.
15. Jiang,Q., S.Akashi, K.Miyake, and H.R.Petty. 2000. Lipopolysaccharide induces physical proximity between CD14 and toll- like receptor 4 (TLR4) prior to nuclear translocation of NF-kappaB [In Process Citation]. *J.Immunol.* 165:3541-3544.
16. Kawasaki,K., S.Akashi, R.Shimazu, T.Yoshida, K.Miyake, and M.Nishijima. 2000. Mouse toll-like receptor 4.MD-2 complex mediates lipopolysaccharide-mimetic signal transduction by Taxol. *J.Biol.Chem.* 2000.*Jan. 28.;275.(4.):2251.-4.*
275:2251-2254.
17. Kleeberger,S.R., S.Reddy, L.Y.Zhang, and A.E.Jedlicka. 2000. Genetic susceptibility to ozone-induced lung hyperpermeability. Role of toll-like receptor 4.
Am.J.Respir.Cell Mol.Biol. 22:620-627.
18. Kurt-Jones, E. A., Popova, L., Kwinn, L., Haynes, L. M., Jones, L. P., Tripp, R. A., Walsh, E. E., Freeman, M. W., Golenbock, D. T., Anderson, L. J., and Finberg, R. W. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. *Nature Immunology* 5, 398-401. 2000.

19. Lien, E., T.K.Means, H.Heine, A.Yoshimura, S.Kusumoto, K.Fukase, M.J.Fenton, M.Oikawa, N.Qureshi, B.Monks, R.W.Finberg, R.R.Ingalls, and D.T.Golenbock. 2000. Toll-like receptor 4 imparts ligand-specific recognition of bacterial lipopolysaccharide. *J.Clin.Invest.* 105:497-504.
20. Lien, E., J.C.Chow, L.D.Hawkins, P.D.McGuinness, K.Miyake, T.Espevik, F.Gusovsky, and D.T.Golenbock. 2000. A novel synthetic acyclic lipid A-like agonist activates cells via the lipopolysaccharide/Toll-like receptor 4 signaling pathway. *J.Biol.Chem.*
21. Matsuguchi, T., T.Musikachoen, T.Ogawa, and Y.Yoshikai. 2000. Gene Expressions of Toll-Like Receptor 2, But Not Toll-Like Receptor 4, Is Induced by LPS and Inflammatory Cytokines in Mouse Macrophages. *J.Immunol.* 165:5767-5772.
22. Matsumura, T., A.Ito, T.Takii, H.Hayashi, and K.Onozaki. 2000. Endotoxin and cytokine regulation of toll-like receptor (TLR) 2 and TLR4 gene expression in murine liver and hepatocytes [In Process Citation]. *J.Interferon Cytokine Res.* 20:915-921.
23. Nattermann, J., X.Du, Y.Wei, D.Shevchenko, and B.Beutler. 2000. Endotoxin-mimetic effect of antibodies against Toll-like receptor 4. *J.Endotoxin Res.* 6:257-264.
24. Nomura, F., S.Akashi, Y.Sakao, S.Sato, T.Kawai, M.Matsumoto, K.Nakanishi, M.Kimoto, K.Miyake, K.Takeda, and S.Akira. 2000. Cutting edge: endotoxin

tolerance in mouse peritoneal macrophages correlates with down-regulation of surface toll-like receptor 4 expression [In Process Citation].

J.Immunol. 2000. Apr. 1.; 164. (7.):3476.-9. 164:3476-3479.

25. Poltorak, A., Smirnova, I., Clisch, R., and Beutler, B. Limits of a deletion spanning *Tlr4* in C57BL/10ScCr mice. *J.Endotoxin Res.* 6(1), 51-56. 2000.
26. Poltorak, A., Ricciardi-Castagnoli, P., Citterio, A., and Beutler, B. Physical contact between LPS and Tlr4 revealed by genetic complementation. *Proceedings of the National Academy of Sciences of the United States of America* 97(5), 2163-2167. 2000.
27. Rehli, M., Poltorak, A., Schwarzfischer, L., Krause, S. W, Andreesen, R., and Beutler, B. PU.1 and interferon consensus sequence binding protein (ICSBP) regulate the myeloid expression of the human Toll-like receptor 4 gene. *Journal of Biological Chemistry* 275(13), 9773-9781. 2000.
28. Rhee, S.H. and D.Hwang. 2000. Murine TOLL-like Receptor 4 Confers Lipopolysaccharide Responsiveness as Determined by Activation of NFkappa B and Expression of the Inducible Cyclooxygenase. *J.Biol.Chem.* 275:34035-34040.
29. Sato, S., F.Nomura, T.Kawai, O.Takeuchi, P.F.Muhlradt, K.Takeda, and S.Akira. 2000. Synergy and cross-tolerance between toll-like receptor (TLR) 2- and TLR4-mediated signaling pathways [In Process Citation]. *J.Immunol.* 165:7096-7101.

30. Smirnova, I., Poltorak, A., Chan, E. K. L., McBride, C., and Beutler, B.
Phylogenetic variation and polymorphism at the Toll-like receptor 4 locus (TLR4).
Genome Biology 1(1), 1-10. 2000.
31. Tapping, R.I., S.Akashi, K.Miyake, P.J.Godowski, and P.S.Tobias. 2000. Toll-Like
Receptor 4, But Not Toll-Like Receptor 2, Is a Signaling Receptor for Escherichia
and Salmonella Lipopolysaccharides. *J.Immunol.* 165:5780-5787.
32. Wang, P.L., Y.Azuma, M.Shinohara, and K.Ohura. 2000. Toll-like Receptor 4-
Mediated Signal Pathway Induced by Porphyromonas gingivalis
Lipopolysaccharide in Human Gingival Fibroblasts.
Biochem.Biophys.Res.Comm. 273:1161-1167.
33. Yang, H., D.W.Young, F.Gusovsky, and J.C.Chow. 2000. Cellular Events Mediated
by Lipopolysaccharide-stimulated Toll-like Receptor 4. MD-2 IS REQUIRED FOR
ACTIVATION OF MITOGEN-ACTIVATED PROTEIN KINASES AND Elk-1.
J.Biol.Chem. 275:20861-20866.
34. Beutler, B. and Poltorak, A. The sole gateway to endotoxin response: how *Lps* was
identified as *Tlr4*, and its role in innate immunity. *Drug Metab.Dispos.* 29, 474-
478. 1-1-2001.
35. Beutler, B., X.Du, and A.Poltorak. 2001. Identification of Toll-like receptor 4
(TLR4) as the sole conduit for LPS signal transduction: genetic and evolutionary
studies. *J.Endotoxin Res.* In press.

36. Bihl,F., L.Lariviere, S.T.Qureshi, L.Flaherty, and D.Malo. 2001. LPS-hyporesponsiveness of mnd mice is associated with a mutation in Toll-like receptor 4. *Genes Immun.* 2:56-59.
37. Byrd-Leifer,C.A., E.F.Block, K.Takeda, S.Akira, and A.Ding. 2001. The role of MyD88 and TLR4 in the LPS-mimetic activity of Taxol. *Eur.J.Immunol.* 31:2448-2457.
38. da Silva,C.J., K.Soldau, U.Christen, P.S.Tobias, and R.J.Ulevitch. 2001. Lipopolysaccharide is in Close Proximity to Each of the Proteins in Its Membrane Receptor Complex: Transfer from CD14 to TLR4 and MD-2. *J.Biol.Chem.*
39. Pridmore,A.C., D.H.Wyllie, F.Abdillahi, L.Steeghs, L.P.van Der, S.K.Dower, and R.C.Read. 2001. A Lipopolysaccharide-Deficient Mutant of *Neisseria meningitidis* Elicits Attenuated Cytokine Release by Human Macrophages and Signals via Toll-like Receptor (TLR) 2 but Not via TLR4/MD2. *J.Infect.Dis.* 183:89-96.
40. Read,R.C., J.Pullin, S.Gregory, R.Borrow, E.B.Kaczmariski, F.S.Di Giovine, S.K.Dower, C.Cannings, and A.G.Wilson. 2001. A Functional Polymorphism of Toll-like Receptor 4 Is Not Associated with Likelihood or Severity of Meningococcal Disease. *J.Infect.Dis.* 184:640-642.
41. Sasu,S., D.LaVerda, N.Qureshi, D.T.Golenbock, and D.Beasley. 2001. Chlamydia pneumoniae and chlamydial heat shock protein 60 stimulate proliferation of human vascular smooth muscle cells via toll-like receptor 4 and p44/p42 mitogen-activated protein kinase activation. *Circ.Res.* 89:244-250.

42. Smiley, S.T., J.A.King, and W.W.Hancock. 2001. Fibrinogen stimulates macrophage chemokine secretion through toll-like receptor 4. *J.Immunol.* 167:2887-2894.
43. Smirnova, I., M.Hamblin, C.McBride, B.Beutler, and A.Di Rienzo. 2001. Excess of rare amino acid polymorphisms in the Toll-like receptor 4 in humans. *Genetics* 158:1657-1664.